REMARKS

Claims 89-100 are pending. With this Amendment, claims 89, 91 and 92 have been amended, and claim 90 has been cancelled. The amendment of claim 89 incorporates the limitations of cancelled claim 90. Amendment of claims 91 and 92 is to correct dependency due to cancellation of claim 90 and amendment of claim 89. Amendment of the specification is to correct a typographical error and to include sequence identifiers. No new matter is believed to have been added.

With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any objection and/or rejection made by the Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded claimed subject matter or embodiments in one or more future or pending continuation and/or divisional applications.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Sequence Listing

Applicants submit herewith a Sequence Listing believed to be in compliance with the requirements of the sequence rules (37 C.F.R. 1.821-1.825). The Examiner stated that there are sequences that are not identified with sequence numbers located in TABLES VI-XV, TABLE B1 and B2, as well as throughout the specification, specifically noting page 36, lines 6 & 52; page 7, lines 12, 21, 22 and 33; page 36, lines 51 & 52; page 37, lines 3-6; and page 55, line 30. The accompanying Sequence Listing addresses these inadvertent omissions, except for the alleged sequences in Tables X, XI, XII, XIII and XIII-A, which Applicants respectfully submit do not fall within the sequence listing requirements of 37 C.F.R. 1.821-1.825. Specifically, the residues listed in Tables X, XI, XIII, XIII-A are individual residues in non-contiguous positions (for e.g., in Table X, HGNN represent residues at non-contiguous sequence positions 10, 14, 18 and 21), and thus do not constitute a sequence within the scope of 37 C.F.R. 1.821-1.825. Table XII does not list any sequences.

Statutory type double patenting

Claims 93 and 96 stand rejected under 35 U.S.C. 101 as allegedly claiming the same invention as that of claim 12 of U.S. Pat. No. 6,040,136 (referred to herein as the '136 patent). The Examiner alleges that claims 93 and 96 of the instant application are anticipated by claim 12 of '136.[1]

Applicants respectfully traverse.

35 U.S.C. 101 prevents two patents from issuing on the same invention. "Same invention" means identical subject matter. A reliable test for double patenting under 35 U.S.C. 101 is whether a claim in the application could be literally infringed without literally infringing a corresponding claim in the patent. That is, is there an embodiment of the invention that falls within the scope of one claim, but not the other, and if there is such an embodiment, then identical subject matter is not defined by both claims and statutory double patenting would not exist. See MPEP Section 804II.A. (emphasis added). An analysis of claim 12 of the '136 patent and instant claims 93 & 96 shows that the claims do not encompass identical subject matter. Claim 12 of the '136 patent (which depends from claim 7, which in turn depends from claim 6, which in turn depends from claim 1) is directed to "a phagemid expression vector, comprising a transcription regulatory element operably linked to a gene fusion encoding a fusion protein, wherein the gene fusion comprises a first gene encoding a polypeptide (wherein the polypeptide is fused to a carboxy terminal domain of a polypeptide encoded by gene III -- *as recited in claim 7*) and a second gene encoding at least a portion of a phage coat protein (wherein the coat protein is encoded by gene III of a filamentous phage -- *as recited in claim 6*), (wherein the fusion gene contains a suppressible stop codon between the first gene and the second gene -- *as recited in claim 12*) the vector not containing a further gene encoding a mature phage coat protein." Instant claim 93 is directed to "a replicable expression vector comprising the gene fusion of claim 89 (which is a gene fusion comprising a first gene encoding a first polypeptide, a second gene encoding at least a portion of a phage coat protein -- as recited in amended claim 89), and a suppressible termination codon between or adjacent to the first and second genes. Instant claim 96 is directed to "a replicable phagemid expression vector comprising the gene fusion of claim 95 (which is a gene fusion comprising a first gene encoding a first polypeptide, a second gene encoding at least a portion of a filamentous bacteriophage coat protein III, and a suppressible termination codon selected from the group consisting of UAG, UAA and UGA between the first and second genes -- as recited in claim 95)." It is clear that claim 12 of the '136 patent does not encompass

[1] For the sake of clarity, Applicants note that "anticipation" is not a proper basis for a statutory double patenting analysis. Applicants further note that the instant application and the patent application from which the '136 patent issued are related in terms of priority dates, and are entitled to the same effective filing date.

the *identical* subject matter as either of instant claims 93 and 96; it is evident that instant claims 93 & 96, and claim 12 of the '136 patent could be literally infringed without literally infringing claim 12 of '136.

Thus, Applicants respectfully request withdrawal of this rejection.

Obviousness-type double patenting

Claims 94, 97, 99 and 100 stand rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 12 and 14 of U.S. Pat. 6,040,136 (hereinafter '136).

Applicants respectfully traverse.

Regarding claim 99, Applicants respectfully submit that claim 99 is not obvious in view of claims 12 and 14 of the '136 patent, as the Examiner has not adequately shown that the ordinary skilled artisan would have been motivated to combine the limitations of claims 12 and 14 to achieve the claimed invention of claim 99. Applicants submit that just because both claims 12 and 14 of the '136 patent are dependent from the same claim is not sufficient evidence for asserting that it would have been obvious to apply the limitations of claim 12 to those of claim 14 of the '136 patent. See Office Action, page 5.

Regarding the rejection of claims 94, 97 and 100, Applicants disagree with the Examiner's reasoning. The Examiner contends that host cells comprising vectors claimed by instant claims 93, 96 and 99 are "representative of the vectors themselves . . . [and t]hus the host cells comprising the vectors in the instant application are anticipated by the claims describing the vectors in the '136 patent."[2] Office Action, page 6. Applicants reiterate the arguments above regarding the double patenting rejection of claims 93 and 96 (both for alleged statutory double patenting) and claim 99 (for alleged non-statutory double patenting). Furthermore, Applicants note that the scope of the instant claims and claims 12 & 14 of the '136 patent are clearly distinguishable. Claims 94, 97 and 100 are directed to host cells, and as the Examiner acknowledged, host cells are not explicitly claimed in the '136 patent.

The Examiner stated that there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. Office Action, page 5 and 6. Applicants submit that this point is not relevant to the instant rejection. Notwithstanding Applicants' points set forth above with respect to the instant rejection, Applicants further submit that it is within Applicants' right to pursue the instant claims despite the issuance of the '136 patent. As stated in MPEP 201.07, "at any time before the patenting or abandonment of or termination of proceedings on his or her earlier nonprovisional application, an applicant may have recourse to filing a continuation in order to introduce into the application *a new set of*

claims and to establish a right to further examination by the primary examiner." Applicants respectfully submit that there is no restriction as to the scope and type of claims that constitute said new set of claims.

Notwithstanding the above, Applicants will execute a terminal disclaimer upon an indication of allowability of these claims.

Rejection under 35 U.S.C. 102

Claims 89-92, 95 and 98 stand rejected under 35 U.S.C. 102(b) as being allegedly anticipated by George et al. (US. Pat. No. 4,673,641).

Applicants respectfully traverse.

As a preliminary matter, Applicants note that claim 90 has been cancelled, rendering rejection of this claim moot. Applicants also note that claim 89 has been amended to recite "a second gene encoding at least a portion of a phage coat protein."

Applicants further note that claims 93, 94, 96, 97, 99 and 100 are not rejected under this section and thus are believed to be free of art.

Applicants respectfully submit that George et al. does not anticipate the pending claims, as it does not teach all the limitations of the claims as required under the law. The Examiner contends that "[i]n the absence of disclosure of a specific antibody and because an antibody is a protein, George et al. also teaches the use of an antibody as the first polypeptide in the gene fusion." Office Action, page 7. Applicants disagree with this reasoning. Applicants assume the Examiner makes this assertion with respect to the rejection of claim 98. The word "protein" is a general term that encompasses a group of polypeptides, one of which polypeptide could be an antibody. Applicants respectfully submit that it is impermissible to extrapolate from the *general* teaching of George et al., which merely refers to a fusion comprising a *protein* without specific teaching of the protein being an antibody[3], to the invention encompassed by claim 98 which contains the *specific* limitation of a first gene encoding an antibody or a fragment thereof. Thus, George et al. fails as anticipatory art with respect to the instant claims.

George et al. also fails to teach the limitation of the second gene encoding at least a portion of a phage coat protein/filamentous bacteriophage coat protein III. The Examiner alleges that "[c]onsidering the definition of 'portion of' as set forth above (see 112 rejections), any amino acid that is present in

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[2] Applicants reiterate the comments in footnote 1 regarding the assertion that host cells comprising the vectors in the instant application are "anticipated" by the related '136 patent.

[3] The Examiner is requested to point to specific parts of George et al. that discloses antibody or fragment thereof if he believes Applicants are mistaken on this point.

bacteriophage coat protein III can serve as a portion of bacteriophage coat protein III ... [and that] since all proteins contain at least one of the same amino acid, the claim as written reads on a gene fusion between any two polypeptides." Office Action, page 7. Applicants respectfully disagree with this reasoning. Applicants note that there is no 112 rejection in the outstanding Office Action (which is properly consecutively numbered from pages 2-10). Notwithstanding this, Applicants submit that one of skill in the art would understand that the phrase "a second *gene* encoding at least a portion of a phage coat protein" (see amended claim 89) and the phrase "a second *gene* encoding at least a portion of a filamentous bacteriophage coat protein III" (see claims 95 and 98) contain the implicit limitation that the second gene encodes a polypeptide that has more than one amino acid. Thus, it is incorrect for the Examiner to suggest that "any amino acid that is present in bacteriophage coat protein III can serve as a portion of bacteriophage coat protein III ... and that since all proteins contain at least one of the same amino acid, the claim as written reads on a gene fusion between any two polypeptides."

In view of the discussion above, Applicants respectfully request that these rejections under 35 U.S.C. §102(b) be withdrawn.

Rejection under 35 U.S.C. 103(a)

Claims 90-92, 95 and 98 stand rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over George et al., in view of Smith (Science 228:1315-1317 (1985)).

Applicants respectfully traverse.

The Examiner contends that "[i]n the absence of disclosure of a specific antibody and because an antibody is a protein, George et al. also teaches the use of an antibody as the first polypeptide in the gene fusion." Again, Applicants assume the Examiner is referring to claim 98. As stated in the discussion of §102 rejection above, while George et al. refers to fusion of proteins *generally*, it does not specifically identify the species of protein in the form of an antibody, thus this reference cannot be used as a teaching or disclosure of the limitation of "antibody" in the pending claims.

Applicants respectfully submit that the combination of George et al. and Smith does not teach the claimed invention. The Examiner acknowledges that George et al. does not describe the use of bacteriophage coat protein III as the second polypeptide in the gene fusion, but contends that George et al. is modified by Smith to include the use of bacteriophage coat protein III in the gene fusion contained within the phagemid expression vector. The Examiner alleges that "the ordinary skilled artisan would have been motivated to combine these teachings in order to provide an efficient means of displaying the polypeptide of the first gene in the fusion at the surface of phagemid particles." Office Action, page 9.

Applicants respectfully point out that the Examiner has not shown that either cited reference, or the art, singly or in combination, suggest or teach the claimed invention. There is no suggestion or teaching to include a suppressible termination codon in a gene fusion, in particular in the context of a gene fusion comprising at least a portion of a phage coat protein. George et al. relates to methods for stabilization and purification of proteins produced in host cell systems, where the methods provide for stabilization of unfused non-bacterial protein that is produced in the same host cell that is producing an aggregate-forming fusion protein or any aggregate-forming protein (see Abstract). A fusion protein altered by inclusion of a chain termination sequence at the junction of the two proteins which comprise the fusion protein is noted as one embodiment of the fusion protein underlying the concept of the method of George et al. However, the primary objective appears to be the production of both an unfused protein as well as a fusion protein (because suppression is significantly less than 100%) in a *single* host cell. See George et al., column 10, lines 32-36. The production of a mix of unfused protein and fusion protein is important in the context of the teachings of George et al., which are based on the notion that fusion proteins are resistant to degradation in the host cell, and that there would be stabilization of any unfused foreign protein produced in the same host cell which is also producing an aggregate-forming protein (George et al. contends that fusion proteins produced at high levels in a host cell tend to form insoluble aggregates). George et al., column 6, lines 34-51. Nowhere in George et al. is there any mention of a fusion protein comprising at least a portion of a phage coat protein or any relevance to phage display technology. Smith et al. does not teach nor suggest a fusion gene containing a suppressible termination codon between or adjacent to a first gene and a second gene encoding at least a portion of a phage coat protein. Thus, neither of the cited references, singly or in combination, teach or suggest the claimed invention.

Applicants respectfully submit that the Examiner has not shown why the skilled artisan would be motivated to combine the cited references to achieve the claimed invention. Claim 89, as amended, is directed to "a gene fusion, comprising a first gene encoding a first polypeptide, a second gene encoding at least a portion of a phage coat protein, and a suppressible termination codon between or adjacent to the first and second genes." Claim 95 is directed to "a gene fusion comprising a first gene encoding a first polypeptide, a second gene encoding at least a portion of a filamentous bacteriophage coat protein III,and a suppressible termination codon selected from the group consisting of UAG, UAA and UGA between the first and second genes." Claim 98 is directed to "a gene fusion comprising a first gene encoding an antibody or a fragment thereof, a second gene encoding at least a portion of a filamentous bacteriophage coat protein III, and a suppressible termination codon selected from the group consisting of UAG, UAA and UGA between the first and second genes." As discussed above, neither George et al. nor Smith et al.

teaches or suggests the feasibility, benefit or utility of the inclusion of a suppressible termination codon as contemplated in the claimed invention. Furthermore, Applicants respectfully submit that prior to the effective filing date of the present application, the art did not contemplate nor suggest the need or utility of having a suppressible termination codon between a polypeptide of interest and a phage coat protein, in particular in the context of phage display technology. A review of the scientific literature pertaining to phage display technology bears this out. For example, two significant articles in the field of phage display technology prior to the effective filing date of the instant application, Smith (*Science* 228:1315:1317 (1985) & Parmley & Smith (*Gene* 73:305-318 (1988)), both of record, neither teach nor suggest inclusion of a suppressible termination codon in a gene fusion between a first polypeptide and at least a portion of a phage coat protein. Without an appreciation of such a need or utility, there would not have been motivation to achieve the presently claimed invention.

In view of the discussion above, Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness. Therefore, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants believe that this application is now in condition for immediate allowance and respectfully request that the outstanding rejections be withdrawn and this case passed to issue. No new matter has been introduced, and entry of these amendments is respectfully requested. Reconsideration and further examination of the claims is respectfully requested.

The Examiner is invited to contact the undersigned at (650) 225-5530 in order to expedite the resolution of any remaining issues.

Respectfully submitted,
GENENTECH, INC.

Date: April 2, 2003

By: _____
Paul Naik, Ph.D.
Reg. No. 49,075

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The paragraph beginning at page 20, line 4, has been amended as follows:

VIII. Growth Hormone Variants and Methods of Use

The cloned gene for hGH has been expressed in a secreted form in [Escherichia cola] Escherichia coli (Chang, C. N>, *et al.*, [1987] Gene 55, 189) and its DNA and amino acid sequence has been reported (Goeddel, *et al.* [1979] Nature 281, 544; Gray *et al.*, [1985] Gene 39, 247). The present invention describes novel hGH variants produced using the phagemid selection methods. Human growth hormone variants containing substitutions at positions 10, 14, 18, 21, 167, 171, 172, 174, 175, 176, 178 and 179 have been described. Those having higher binding affinities are described in Tables VII, XIII and XIV. The amino acid nomenclature for describing the variants is shown below. Growth hormone variants may be administered and formulated in the same manner as regular growth hormone. The growth hormone variants of the present invention may be expressed in any recombinant system which is capable of expressing native or met hGH.

The paragraph beginning at page 7, line 11, has been amended as follows:

FIGURE 5. Amino acid substitutions at positions 172, 174, 176 and 178 of hGH (The notation, e.g. KSYR, denotes hGH mutant 172K/174S/176Y/178R.) found after sequencing a number of clones from rounds 1 and 3 of the selection process for the pathways indicated (hGH elution; Glycine elution; or Glycine elution after pre-adsorption). Non-functional sequences (i.e. vector background, or other prematurely terminated and/or frame-shifted mutants) are shown as "NF". Functional sequences which contained a non-silent, spurious mutation (i.e. outside the set of target residues) are marked with a "+". Protein sequences which appeared more than once among all the sequenced clones, but with different DNA sequences, are marked with a "#". Protein sequences which appeared more than once among the sequenced clones and with the same DNA sequence are marked with a "*". Note that after three rounds of selection, 2 different contaminating sequences were found; these clones did not correspond to cassette mutants, but to previously constructed hormone phage. The pS0643 contaminant corresponds to wild-type hGH-phage (hGH "KEFR"(SEQ ID NO:44)). The pH0457 contaminant, which dominates the third-round glycine-selected pool of phage, corresponds to a previously identified mutant of hGH, "KSYR."

The amplification of these contaminants emphasizes the ability of the hormone-phage selection process to select for rarely occurring mutants. The convergence of sequences is also striking in all three pathways: R or K occurs most often at positions 172 and 178; Y or F occurs most often at position 176; and S, T, A, and other residues occur at position 174.

The paragraph beginning at page 7, line 31, has been amended as follows:

FIGURE 7. Sequences from phage selected on hPRLbp-beads in the absence of zinc. The notation is as described in Figure 5. In contrast to the sequences of Figure. 6, these sequences appear more hydrophilic. After 4 rounds of selection using hGH elution, two clones (ANHQ (SEQ ID NO:45), and TLDT/171V (SEQ ID NO:108)) dominate the pool.

Table VI, beginning at page 34, line 1, has been amended as follows:

Table VI.

Non-selected (pH0529E) clones with an open reading frame.
The notation, e.g. TWGS, denotes the hGH mutant 172T/174W/176G/178S. Amber (TAG) codons, translated as Glu in XL1-Blue cells are shown as ε.

Kε NT (SEQ ID NO: 46)	**KTEQ (SEQ ID NO: 59)**	**CVLQ (SEQ ID NO:72)**
TWGS (SEQ ID NO: 47)	**NNCR (SEQ ID NO: 60)**	**EASL (SEQ ID NO: 73)**
Pε ER (SEQ ID NO: 48)	**FPCL (SEQ ID NO: 61)**	**SSKE (SEQ ID NO: 74)**
LPPS (SEQ ID NO: 49)	**NSDF (SEQ ID NO: 62)**	**ALLL (SEQ ID NO: 75)**
SLDP (SEQ ID NO: 50)	**HRPS (SEQ ID NO: 63)**	**PSHP (SEQ ID NO: 76)**
QQSN (SEQ ID NO: 51)	**LSLε (SEQ ID NO: 64)**	**SYAP (SEQ ID NO: 77)**
GSKT (SEQ ID NO: 52)	**NGSK (SEQ ID NO: 65)**	**ASNG (SEQ ID NO: 78)**
TPVT (SEQ ID NO: 53)	**LTTE (SEQ ID NO: 66)**	**EANN (SEQ ID NO: 79)**
RSRA (SEQ ID NO: 54)	**PSGG (SEQ ID NO: 67)**	**KNAK (SEQ ID NO: 80)**
LCGL (SEQ ID NO:.55)	**LWFP (SEQ ID NO: 68)**	**SRGK (SEQ ID NO: 81)**
TGRL (SEQ ID NO: 56)	**PAGS (SEQ ID NO: 69)**	**GLDG (SEQ ID NO: 82)**
AKAS (SEQ ID NO: 57)	**GRAK (SEQ ID NO: 70)**	**NDPI (SEQ ID NO: 83)**
GNDD (SEQ ID NO: 58)	**GTNG (SEQ ID NO: 71)**	

The paragraph beginning at page 36, line 4 has been amended as follows:

The results for a number of hGH mutants, selected by different pathways (Fig. 6) are shown in Table VII. Many of these mutants have a tighter binding affinity for hGHbp than wild-type hGH. The most

improved mutant, KSYR (SEQ ID NO:84), has a binding affinity 5.6 times greater than that of wild-type hGH. The weakest selected mutant, among those assayed was only about 10-fold lower in binding affinity than hGH.

The paragraph beginning at page 36, line 48 has been amended as follows:

Additive and non-additive effects on binding

At some residues, substitution of a particular amino acid has essentially the same effect independent of surrounding residues. For example, substitution of F176Y in the background of 172R/174S reduces binding affinity by 2.0-fold (RSFR (SEQ ID NO:85) vs. RSYR (SEQ ID NO:88)). Similarly, in the background of 172K/174A the binding affinity of the F176Y mutant (KAYR (SEQ ID NO:89)) is 2.9-fold weaker than the corresponding 176F mutant (KAFR; Cunningham and Wells, 1989).

The paragraph beginning at page 37, line 1 has been amended as follows:

On the other hand, the binding constants determined for several selected mutants of hGH demonstrate non-additive effects of some amino acid substitutions at residues 172, 174, 176, and 178. For example, in the background of 172K/176Y, the substitution E174S results in a mutant (KSYR (SEQ ID NO:84)) which binds hGHbp 3.7-fold tighter than the corresponding mutant containing E174A (KAYR (SEQ ID NO:89)). However, in the background of 172R/176Y, the effects of these E174 substitutions are reversed. Here, the E174A mutant (RAYR (SEQ ID NO:86)) binds 1.5-fold tighter than the E174S mutant (RSYR (SEQ ID NO:88)).

Table VII, beginning at page 36, line 10, has been amended as follows:

Table VII.
Competitive binding to hGHbp

The selected pool in which each mutant was found is indicated as 1G (first glycine selection), 3G (third glycine selection), 3H (third hGH selection), 3* (third selection, not binding to hPRLbp, but binding to hGHbp). The number of times each mutant occurred among all sequenced clones is shown ().

Mutant	Kd (nM)	Kd(mut)/Kd(hGH)	Pool
KSYR (6) (SEQ ID NO:84)	0.06 + 0.01	0.18	1G,3G
RSFR (SEQ ID NO:85)	0.10 + 0.05	0.30	3G
RAYR (SEQ ID NO:86)	0.13 + 0.04	0.37	3*
KTYK (2) (SEQ ID NO:87)	0.16 + 0.04	0.47	H,3G
RSYR (3) (SEQ ID NO:88)	0.20 + 0.07	0.58	1G,3H,3G
KAYR (3) (SEQ ID NO:89)	0.22 + 0.03	0.66	3G
RFFR (2) (SEQ ID NO:90)	0.26 + 0.05	0.76	3H
KQYR (SEQ ID NO:91)	0.33 + 0.03	1.0	3G
KEFR= wt (9)	0.34 + 0.05	1.0	3H,3G,3*
RTYH (SEQ ID NO:92)	0.68 + 0.17	2.0	3H
QRYR (SEQ ID NO:93)	0.83 + 0.14	2.5	3*
KKYK (SEQ ID NO:94)	1.1 + 0.4	3.2	3*
RSFS (2) (SEQ ID NO:95)	1.1 + 0.2	3.3	3G,*
KSNR (SEQ ID NO:96)	3.1 + 0.4	9.2	3*

Table B1, beginning at page 60, line 1, has been amended as follows:

Table B1

Sequences of eluted phage after 2 rounds of selective enrichment.

All protein sequences should be of the form AA**TRQ, where * represents a randomised codon. In the table below, the randomised codons and amino acids are underlined and in bold.

After round 2:

Sequence ~~(SEQ ID Nos. 32-37)~~	No. of occurrences	
* *		
A A **H Y** T R Q (SEQ ID NO:97) ... GCT GCT **CAC TAC** ACC CGG CAA ... (SEQ ID NO:32)	2	
A A **H M** T R Q (SEQ ID NO:98) ... GCT GCT **CAC ATG** ACC CGG CAA ... (SEQ ID NO:33)	1	
A A **L H** T R Q (SEQ ID NO:99) ... GCT GCT **CTC CAC** ACC CGG CAA ... (SEQ ID NO:34)	1	
A A **L H** T R Q (SEQ ID NO:99) ... GCT GCT **CTG CAC** ACC CGG CAA ... (SEQ ID NO:35)	1	
A A **H T** R Q (SEQ ID NO:100) ... GCT GCT **CAC ACC** CGG CAA ... (SEQ ID NO:36)	1	#
A A **? H** T R Q (SEQ ID NO:101) ... GCT GCT **??? CAC** ACC CGG CAA (SEQ ID NO:37)	1	##
... wild-type pDM0454	3	

- spurious deletion of 1 codon within the cassette
- ambiguous sequence

Table B2 beginning at page 61, line 1, has been amended as follows:

Table B2

Sequences of eluted phage after 3 rounds of selective enrichment.

All protein sequences should be of the form AA**TRQ, where * represents a randomised codon. In the table below, the randomised codons and amino acids are underlined and in bold.

After round 3:

Sequence ~~(SEQ ID Nos. 38-43)~~	No. of occurrences	
* * A A **H Y** T R Q (SEQ ID NO:97) ... GCT GCT **CAC TAT** ACG CGT CAG ...(SEQ ID NO:38)	2	#
A A **L H** T R Q (SEQ ID NO:99) ... GCT GCT **CTC CAC** ACC CGG CAA ...(SEQ ID NO:34)	2	
A A **Q H** T R Q (SEQ ID NO:102) ... GCT GCT **CAG CAC** ACC CGG CAA ...(SEQ ID NO:39)	1	
A A **T H** T R Q (SEQ ID NO:103) ... GCT GCT **ACG CAC** ACC CGG CAA ...(SEQ ID NO:40)	1	
A A **H S** R Q (SEQ ID NO:104) ... GCT GCT **CAC TCC** CGG CAA ... (SEQ ID NO:41)	1	
A A **H H** T R Q (SEQ ID NO:105) ... GCT GCT **CAT CAT** ACC CGG CAA (SEQ ID NO:42)	1	##
A A **H F** R Q (SEQ ID NO:106) ... GCT GCT **CAC TTC** CGG CAA ... (SEQ ID NO:43)	1	
A A **H T** R Q (SEQ ID NO:100) ... GCT GCT **CAC ACC** CGG CAA ... (SEQ ID NO:36)	1	

- contaminating sequence from pDM0411
- contains the "illegal" codon CAT - T should not appear in the 3rd position of a codon.

The paragraph beginning at page 55, line 1, has been amended as follows:

Construction of a hGH-substrate-phage vector

The sequence of the linker region in pS0132 was mutated to create a substrate sequence for A64SAL subtilisin, using the oligonucleotide 5'-TTC-GGG-CCC-TTC-GCT-GCT-CAC-TAT-ACG-CGT-CAG-TCG-ACT-GAC-CTG-CCT-3' (SEQ ID NO:27). This resulted in the introduction of the protein sequence Phe-Gly-Pro-Phe-Ala-Ala-His-Tyr-Thr-Arg-Gln-Ser-Thr-Asp (SEQ ID NO:107) in the linker region between hGH and the carboxy terminal domain of gene III, where the first Phe residue in the above sequence is Phe191 of hGH. The sequence Ala-Ala-His-Tyr-Thr-Agr-Gln (SEQ ID NO:97) is known to be a good substrate for A64SAL subtilisin (Carter et al (1989), supra). The resulting plasmid was designated pS0640.

In the claims:

Claim 90 has been cancelled without prejudice or disclaimer.
Claims 89, 91 and 92 have been amended as follows.

89. (Once Amended) A gene fusion, comprising a first gene encoding a first polypeptide, a second gene encoding [a second polypeptide,] at least a portion of a phage coat protein, and a suppressible termination codon between or adjacent to the first and second genes.

91. (Once Amended) The gene fusion of claim [90] 89, wherein the suppressible termination codon is UAG, UAA or UGA.

92 (Once Amended) The gene fusion of claim [90] 89, wherein the phage coat protein is a filamentous bacteriophage coat protein III or a portion thereof.

CLEAN SET OF PENDING CLAIMS

89. A gene fusion, comprising a first gene encoding a first polypeptide, a second gene encoding at least a portion of a phage coat protein, and a suppressible termination codon between or adjacent to the first and second genes.

91. The gene fusion of claim 89, wherein the suppressible termination codon is UAG, UAA or UGA.

92 The gene fusion of claim 89, wherein the phage coat protein is a filamentous bacteriophage coat protein III or a portion thereof.

93. A replicable expression vector comprising the gene fusion of claim 89.

94. A host cell comprising the vector of claim 93.

95. A gene fusion comprising a first gene encoding a first polypeptide, a second gene encoding at least a portion of a filamentous bacteriophage coat protein III, and a suppressible termination codon selected from the group consisting of UAG, UAA and UGA between the first and second genes.

96. A replicable phagemid expression vector comprising the gene fusion of claim 95.

97. A host cell comprising the vector of claim 96.

98. A gene fusion comprising a first gene encoding an antibody or a fragment thereof, a second gene encoding at least a portion of a filamentous bacteriophage coat protein III, and a suppressible termination codon selected from the group consisting of UAG, UAA and UGA between the first and second genes.

99. A replicable phagemid expression vector comprising the gene fusion of claim 98.

100. A host cell comprising the vector of claim 99.